AstraZeneca

Date: October 26, 2006

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD, 20852

Re: Docket No. 2006D-0331
Response to FDA Call for Comments
Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors;
Exception from Informed Consent Requirements for Emergency Research

Dear Sir or Madam:

Reference is made to the August 25, 2006 Federal Register notice announcing the request for comments on Docket No. 2006D-0331 entitled Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors; Exception from Informed Consent Requirements for Emergency Research. AstraZeneca has reviewed this draft guidance and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Melissa Cavuto, Associate Director, at (302) 886-2428

Sincerely,

Gary Cooper, Director
Regulatory Affairs
Telephone: (302) 885-1809
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Enclosure

US Regulatory Affairs
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Draft Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors; Exception from Informed Consent Requirements for Emergency Research

General Comments

- Comment 1

  What would be the impact regarding HIPAA and/or state privacy law? Will it conflict or complicate? How is HIPAA/privacy authorization handled when consent is waived?

- Comment 2

  Below are identified items for clinical trial disclosure on publicly accessible web sites:

<u>Public disclosure before the study begins:</u>

◦ It does not prescribe all the data elements to disclose, but includes some general points to cover

◦ Suggest clarifying that appropriate information should include a risk/benefit description for any drug.

◦ Disclosure could include information beyond the protocol and include the Investigator Brochure (IB) and the Informed Patient Consent (IPC), this may impact on Intellectual Property (IP) issues

The timing for prospective registration is different from the current AstraZeneca position: Before the trial begins the guidance includes:

◦ Sponsor should submit materials to the IRB for review prior to disclosure

◦ Sponsor must provide 'proof' of disclosure to the FDA

◦ The forum and media recommendations extend beyond registration on a publicly accessible web site (advertisements in newspapers in English/local language, presentations, letters, meetings)

<u>Public disclosure after the study is completed:</u>

◦ Sponsor should submit materials to the IRB for review prior to disclosure

◦ Sponsor must provide 'proof' of disclosure to IRB, and that the information is sufficient

Docket Number 2006D-0331, Response to FDA Call for Comments: Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors; Exception from Informed Consent Requirements for Emergency Research.

- Comment 3

  Comments that are focused solely from the IP perspective:

  ◦ The **community consultation** provides communities opportunity to comment on the proposed study, the sponsor would need to review any potential patent opportunities before moving into any community consultations. Since the community obviously will be involved before a trial will be disclosed, timing will be crucial for internally evaluating and taking any measure to secure patent opportunities if any seem to exist

Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors; Exception from Informed Consent Requirements for Emergency Research		
Section	**Page**	**Comment or proposed replacement text**
Introduction	1	How is unproven or unsatisfactory treatment defined/documented? Who decides what is unproven/unsatisfactory? Suggest defining as circumstances in which there are no FDA-approved therapies, or in which the investigational treatment offers a potential significant clinical benefit in terms of efficacy, safety or convenience.
Introduction	2	An IND for each study seems onerous, particularly if we are at a Phase III situation where there are likely to be 2 similar studies. While it may be reasonable to have each protocol pre-reviewed, a new IND seems like it could be excessive.
II Study Design Prospect of Direct Benefit	4	The guidance does not specify the benefits of life saving but diminished quality; i.e., vegetative state. Is that a justified risk? What standard of care is the sponsor responsible for and for how long if diminished quality of life after treatment? How will they distinguish if treatment was directly related?
II Study Design Subject Exclusion	4	In the subject exclusion section, suggest changing the last sentence "such as an individual's medical identification bracelets or necklaces…" to "such as an individual's personal identification cards, medical identification bracelets or necklaces…"
II Study Design Study Design	5	The statement regarding if placebo is used, standard of care is also provide arguably contradicts previous statements indicating that standard of care is unproven or unsatisfactory. It may be useful to have an example where no treatment at all is provided.
III Therapeutic	6	What is written is reasonable, but very vague. What should be done for a drug with a narrow time window to initiate therapy, but has a long treatment period (i.e., days to weeks)? What if

Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors; Exception from Informed Consent Requirements for Emergency Research		
Section	**Page**	**Comment or proposed replacement text**
Window Contact of Family Members		family members cannot be contacted at all during the treatment period to confirm consent? How many contacts must be made? How many different family members should be contacted (i.e., spouse, and if not available, then oldest child or all children, and then parents)? Do they leave a message for the family member if they cannot be reached? If so, how much time between message and initiation of treatment? Suggest documenting something regarding scenario where message is left, treatment initiated and family member returns call with objection (during or after treatment). Suggest that central IRBs may be used provided they adopt some mechanism for local input.
IV IRB Responsibilities General	6	IRB: by the requirement for community consultation, it appears that this forces the issue of only using local, rather than central IRBs (who presumably do not know the details of the local communities). Is this meant to exclude centers that do not have a local IRB and would instead opt for a central IRB? (IRB selection says that the local IRB has to agree to delegate this away - what if there is no local IRB?)
IV IRB Responsibilities General	7	If a subject discontinues, what are the risks of stopping treatment? What is the likelihood of successfully implementing other treatment? Suggest documenting a general statement regarding this scenario.
IV IRB Responsibilities General	8	3rd sub-bullet, clarify to state during the time allotted "within" the therapeutic window. Suggest that the phrase "at least" be deleted from 1st bullet, 5th sub-bullet may be used provided they adopt some mechanism for local input.
IV IRB Responsibilities General	8	Can the DMC be set up in conjunction with the sponsor (particularly if there is a multicenter study and the desire to centralize data)? Is a sponsor DMC sufficient (assuming it is an independent committee)? If each site is to have their own DMC, who will assume the cost? How are discrepancies in remits and conclusions handled?
IV IRB Responsibilities General	8	What is to be done in situation of a multisite/multi-IRB study and there is disagreement on the approvability of the study, and different IRBs request different (and contradictory) changes to the study procedures?
IV IRB	8	How is "promptly" defined in regards to disclosing data? What are the expectations from the sponsor? What evidence of public

Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors; Exception from Informed Consent Requirements for Emergency Research		
Section	**Page**	**Comment or proposed replacement text**
Responsibilities General		disclosure is required?
VI Sponsor Responsibilities	10	Suggest clarifying that the monitoring referred to in the 5th bullet fall under the usual definitions of how a sponsor would monitor all important study activities.
VIII Community Consultation and Public Disclosure General	12	Community Consultation: How would IRBs ensure consistent messages at the public disclosures? How would AstraZeneca become aware of all messages to the public? There is a concern over public disclosures of isolated events (SAEs, etc.) versus trends- media may exaggerate/sensationalize- litigation and public perception issues. Study start-up times may be longer in order to prepare materials. There may be increased costs if there is a need to pay for speakers and meetings for the community consultations and public disclosures. There may be an appearance of coercion or incentives if there is a need to pay for the community consultations, public disclosures. How will the public disclosure post trial affect the sponsor's ability to publish results (if made public too soon)? What parameters does a sponsor have regarding confidentiality measures considering the community consultation is a public venue and the participants will not be bound by the institutional confidentiality agreement? Request addition of guidance on use of both telephone and electronic community contact options; e.g., web sites, to obtain community consultation in situations where face-to-face community consultation may be difficult or unsuccessful. Request addition of guidance on proceeding with the study if IRB documents that reasonable community consultation attempts have not resulted in community feedback. Request guidance on documentation requirements for addressing community feedback.
VIII Community Consultation and Public Disclosure A. Community Consultation	13	Do IRB's have experience in performing community consultations? There appears to be a risk that the process of getting this consultation done (particularly in a multicenter trial) may be so long that the by the time this work is done, the initial agreements may be outdated. Is it practical to assume that the target population would even participate in a community consultation (i.e., to study traumatic brain injury, is it expected that subjects who ride motorcycles, bicycles, participating in sports, or who might have a fall or be hit by something be likely

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Section	**Page**	**Comment or proposed replacement text**
		to be the ones to attend such meetings?)
VIII Community Consultation and Public Disclosure Content	14	What sort of timeframe does the community have to consider options and "opt out" of treatment? What if someone is visiting from out of town and has not been informed of the treatment but would be eligible? What if the subject does not have identifying information on them?
VIII Community Consultation and Public Disclosure The Roles of the Sponsor, Clinical Investigator, and IRB in Community Consultation	14	What if the subject's family does not speak English and there is no translator?
VIII Community Consultation and Public Disclosure Content	17	It seems improbable that the average person will buy a warning bracelet that says they do not want to participate in a study (i.e., traumatic brain injury)
VIII Community Consultation and Public Disclosure Content	17	Do potential subjects have to be in a certain age range? What if there is no identifying information on the subject?
VIII Community Consultation and Public Disclosure 2. Public Disclosure After the Study is Completed	19	Public Disclosure: The guideline says the sponsor is responsible for providing the study results at a community level (in addition to any publications) and recommends two different approaches to disclose results. Is this practical? What is a reasonable period of time for public disclosure after the study is completed? Who defines?
IX Contact of Legally Authorized Representative or Family Members A. Prior To	20	Are the definitions of "family member" etc. used here the same as that applied by hospitals for other informed consent issues?

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Section	**Page**	**Comment or proposed replacement text**
Administration of the Test Article		
IX Contact of Legally Authorized Representative or Family Members Informed Consent Document	20	Will the consent form be abbreviated in consideration of the time sensitivity? Can family members consent over the phone? Would the conversation be recorded?
IX Contact of Legally Authorized Representative or Family Members Opportunity To Object	21	It could be perceived that the researcher is coercive in the decision making process with family members that disagree. Is there standard conduct regarding the researchers contributions to the decision making process?
IX Contact of Legally Authorized Representative or Family Members B. After Administration of the Test Article	21	The following scenario does not appear to be addressed: A legally authorized representative signs the consent following the administration of the device/Investigational Product, the subject's condition subsequently improves and allows appropriate consent by the subject. Procedures should be in place to then consent the subject.